DEPARTMENT OF HEALTH & HUMAN SERVICES

M2276n

Food and Drug Administration
Rockville MD 20857

DEC 18 1998

**WARNING LETTER**

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

Dr. Alex Krauer
Chairman of the Board
Novartis AG
Postfach
CH-4002 Basel, Switzerland

During the period of August 24-28, 1998, an investigator from the U.S. Food and Drug Administration conducted an inspection of your facility located at Lichstrasse 35, Basel, Switzerland, to determine your firm's compliance with the Postmarketing Adverse Drug Experience (PADE) reporting requirements of Section 505(k)(1) of the Federal Food, Drug and Cosmetic Act (the Act) and Title 21 Code of Federal Regulations Part 314.80. Inspectional coverage was also given under Title 21 Code of Federal Regulations Part 211, Current Good Manufacturing Practice for Finished Pharmaceuticals.

Based on our inspection, we conclude that your firm failed to comply with the regulations cited above, as follows:

**PADE Regulations:**

- Your firm failed to submit to the FDA serious and unlabeled adverse drug experience reports within 15 calendar days of initial receipt of the information.

  Examples:

| Product | Mfr. Ctl.# | Date Received by Manufacturer | Date Sent to FDA |
|---|---|---|---|
| Leponex | D/97/02802/LEX | 8/11/97 | 9/11/98 |
| Hydergyne | J/97/00853/HYG | 8/22/97 | 9/11/98 |
| Clozaril | GB/97/01158/LEX | 10/21/97 | 9/11/98 |
| Sandimmune | J/97/01173/SIM | 10/23/97 | 9/11/98 |

| | | | |
|---|---|---|---|
| Tareg | 98F10505 | 6/19/98 | 9/11/98 |
| Carbamazepine | 98HQ10099 | 2/3/98 | 9/11/98 |
| Voltaren | 98TR10000 | 12/31/97 | 9/11/98 |
| Diovan | 97D10438 | 8/18/97 | 9/11/98 |

In addition, you advised FDA that, during the time period of August 1997 through August 1998, approximately nine (9) percent of your firm's 15-day reports were submitted beyond the required time frames.

- Incomplete Medwatch forms were submitted. The name of the initial reporter was not consistently included in the Medwatch form.

  For example:

| Product | Mfr. Ctl. # |
|---|---|
| Lamisil | GB/98/00229/LAS |
| Tareg | 98F-10505 |
| Leponex | D/97/02802/LEX |
| Sandimmun | J/97/01173/SIM |
| Leponex | D/97/02501/LEX |
| Clozaril | GB/97/01158/LEX |

Please note that similar deficiencies involving late reporting and incomplete Medwatch forms were found during an inspection of your Summit, New Jersey facility, conducted during the period of September 4 through October 1, 1997. After completion of that inspection your firm promised global corrective actions.

**CGMP Regulations:**

- The complaint procedures are deficient in that they do not include provisions that allow for the review and determination of an investigation by the Quality Control Unit as required by 21 CFR 211.198(a). There were one hundred and fifty lack of efficacy complaints and eighty-eight efficacy medical effect complaints (efficacy and/or adverse event related quality assurance complaints) that had not been forwarded to the Quality Control Unit for follow-up

evaluation.

- The firm's procedures designed to evaluate annually the quality standards of each drug product distributed are deficiently written in that they do not include the review of medical complaints as required by 21 CFR 211.180(e)(2).

Dr. John Milander's letters to FDA dated September 10 and October 29, 1998, indicated that your firm has initiated a number of corrective actions. We note that as part of your corrective action plan, additional quality control monitoring procedures related to adverse drug experience reporting will be implemented by the Safety Quality Assurance Units. We request that you provide details regarding these procedures including a timetable for implementation of each step.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. You should take prompt action to correct these deviations. If you wish to continue to ship your products to the United States, it is your responsibility to assure compliance with all U.S. standards for Current Good Manufacturing Practices for Pharmaceutical Manufacturers and the Postmarketing Adverse Drug Experience Reporting Regulations.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific quality control monitoring procedures you plan to develop and implement to assure the timely submission of all required PADE reports. You may submit your response to: U.S. Food and Drug Administration, 7520 Standish Place, Rockville, MD 20855-2737, Attn.: Nancy Haggard, Postmarketing ADR Manager, Division of Prescription Drug Compliance and Surveillance (HFD-330).

We have received letters dated October 29, 1998 and November 16, 1998 from Mr. Ronald Califre and Ms. Debbie Wilson of your firm requesting to meet with us on this matter. We will be contacting Mr. Califre and Ms. Wilson to schedule a suitable date and time for a meeting at our office to discuss the inspectional findings and corrective action plan.

Sincerely,

Lana Ogram, Director
Division of Prescription
Drug Compliance and
Surveillance, HFD-330

Joseph C. Famulare, Director
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